III. Amended Title of the Specification and Canceled Claim 3

The title of the specification has been amended to a title more descriptive of the claimed subject matter and the cross-reference to related applications has been updated. Support for the amendment to the title can be found at at least page 3, lines 5-24 of the specification which discloses that the neurotoxic component can be used in the method of the present invention.

Claim 3 is hereby canceled without prejudice to further prosecution at a later date.

IV. Denial of Domestic Priority under 35 U.S.C. Section 120

The Office Action denied priority of claims 1 to 5 under 35 U.S.C. section 120 to parent application 08/173,996, filed December 28, 1993.

Priority to parent application serial number 09/176,996, filed December 28, 1993 ("the '996" application) was denied because as viewed by the Office Action the specification of the '996 application provides neither section 112, first paragraph written description nor enablement to claims 1-5.

Applicants have amended claims independent claims 1 and 5 and added new claims 29-77. Applicants have amended the claims so that all the pending claims are limited to subject matter disclosed by the '996 application. All claims now encompass a claim scope which complies with both the written description and enablement requirements of section 112, as argued below and as supported by the enclosed Brin declaration. Hence, the denial of priority should be withdrawn and priority for the pending claims as amended granted to the '996 application.

The '996 Application Provides Section 112, First Paragraph Written Description for Claims 1-2, 4-5 and 29-77, as Amended

A. Introduction

Page 3 of the Office Action states "The specification is limited to the use of 'botulinum toxin type A' rather than pure botulinum toxin or complex free botulinum toxin...the disclosure does not teach nor imply that only the 150kda component is utilized".

Additionally, The Office Action notes the disclosure in the specification of the botulinum toxin complex products DYSPORT and BOTOX and states that the specification does not distinguish between a botulinum toxin complex and the neurotoxic component (i.e. "pure toxin") of a botulinum toxin complex.

Respectfully, the rejection is in error and should be withdrawn at least because: (1) all claims have been amended to limit to the claims to subject matter which is supported by the '996 application, and; (b) a proper appreciation of the '996 application reveals that the '996 application discloses both the botulinum toxin complex and the neurotoxic component as well as the various serotypes, be they in the form of the complex or the neurotoxic component. The '996 application is clearly all about the neurotoxic component and use of a botulinum toxin complex or of the neurotoxic component by itself are separate embodiments of the teachings of the '996 application.

B. Written Description of the Claimed Invention

Claim 1 and 5 has been amended. Claims 29-77 have been added. The independent claims are claims 1, 5 and 29. All claims (claims 1-2, 4-5 and 29-77) are limited to a method for treating a spastic muscle. The claimed method of claim 1 carried out by administering to a patient with a spastic muscle a therapeutically effective amount of the neurotoxic component of a botulinum toxin to thereby treat the spastic muscle. The neurotoxic component administered to the patient has been purified from a botulinum toxin obtained by fermenting a *Clostridium botulinum* bacterium. Claim 5 is limited to a method in which there is administered "the neurotoxic component of only a botulinum toxin type A Claim 28 recites a method comprising administration of "the neurotoxic component of a single botulinum toxin type".

Each element of all claims 1-5, as amended, is fully supported by the parent '996 application on at least the six bases set forth below. Support for new claims 29-77 is addressed in a subsequent section of this response:

1. First, the disclosure on page 3, lines 5-24 of the '996 application comprises two paragraphs of important disclosure The first paragraph (lines 5-14 on page 3 of the '996 application) clearly states that: (a) there is a neurotoxic component of a botulinum toxin ("The neurotoxic component of botulinum toxin"); (b) that the

neurotoxic component has a molecular weight of about 150 kD; (c) that the 150 kD neurotoxic component is in the form of a dichain ("a short polypeptide chain of about 50 kD...and a larger polypeptide chain of about 100 kD..."), and; (d) the neurotoxic component is responsible for the toxic properties of a botulinum toxin (the "short polypeptide chain [of the neurotoxic component] is considered to be responsible for the toxic properties of the toxin...").

The second paragraph (lines 16-24 on page 3 of the '996 application) discloses that the neurotoxic component can be in the form of a single chain, as opposed to a dichain form, and that "Both the single and the dichain (forms of the neurotoxic component) are useful in the method of the present invention" (text in parenthesis added).

Thus, there can not be the slightest doubt that the '996 application of the present patent application does indeed disclose that a botulinum toxin comprises a neurotoxic component and that therapeutic use of the neurotoxic component is part of the "present invention", since the '996 application states "both the single and the dichain forms (i.e. both forms of the neurotoxic component) are useful in the present invention".

The '996 application discloses and is directed to therapeutic methods for treating a wide variety of spastic muscles. For example, page 10, line 23-24 discloses treating a spastic facial muscle; page 13, line 26 and page 19, line 11 treating a spastic hand muscle; page 13, line 26 treating a spastic head muscle; page 11, line 25 treating a spastic neck muscle; page 15, line 6 treating a spastic vocal cord muscle; Example 6 on page 17, at lines 9-25 discloses treating a spastic smooth muscle, which can be eg a spastic smooth muscle sphincter of the gastrointestinal, urinary or rectal system; page 17, line 35 continuing to page 18, line 1 discloses treating a spastic jaw muscle; page 18, line 12 treating a spastic thigh muscle; Example 9 on page 19 at lines 1-15 discloses treating a

spastic wrist, forearm, or leg muscle, and; page 19, line 22 and page 20, line 6 discloses treating a spastic throat muscle

Additionally, the '996 application states that "both the single and the dichain forms (of the neurotoxic component) are useful in the present invention". Hence, it is clear that the '996 application provides written description sufficient under section 112(1) to support claims directed to use of the neurotoxic component to treat a spastic muscle.

Significantly, both the existence of the neurotoxic component and that the neurotoxic component is responsible for the biological activity of a botulinum toxin was known in the prior art:

> "Each neurotoxin is synthesized as a single chain polypeptide with a molecular weight of approximately 150,000. In the immediate post-translational stage the neurotoxins have diminished biological activity. When exposed to proteases, the single chain toxins are nicked to yield dichain molecules in which a light chain (Mr ~50,000) is linked by a disulfide bond to a heavy chain (Mr ~1000,000). This represents the biologically active form of the toxin." Quoted from page 6 of Simpson L., *Current Concepts of the Mechanism of Action of Clostridial Neurotoxins*, which is pages 5-15 of DasGupta B., Botulinum and Tetanus Neurotoxins, Plenum Press, New York (1993) (attached as Exhibit A).

See also Boroff D., et al., *Amino acid analysis of the isolated and purified components from crystalline toxin of Clostridium botulinum type A*, Infect Immun 1970 Nov;2(5):679-680 (attached as Exhibit B) ("type A toxin is indeed a mixture of protein…The α component had a molecular weight of 150,000…and had virtually all of the toxicity of crystalline toxin") (page 679, left hand side column), and; Dasgupta B., et al., *Purification of Clostridium botulinum type A toxin*, Biochimica et Biophysica Acta 1970 Aug;214(2):343-9 (attached as Exhibit C) ("The crystalline toxin of mol. wt. 900 000 (page 343, Introduction paragraph), "the purified toxin (has a) molecular weight of 150 000 (page 343, Summary paragraph).

Clearly, the prior art (including the Jankovic (1991) publication (attached as Exhibit D) which was incorporated by reference into the '996 application at page 2, line 29-33) taught the existence of the neurotoxic component, and thereby support the disclosure at page 3, lines 5-24 of the '996 application.

2. Second, the '996 application of the instant application states at page 2, lines 24-26 of the '996 application that: "The term Botulinum toxin is a generic term embracing the family of toxins produced by the anaerobic bacterium *Clostridium botulinum*…" (page 2, lines 24-26 of the '996 application). It was known to the prior art that the family of botulinum toxins naturally produced by the Clostridium bacterium includes the neurotoxic component (molecular weight about 150,000) by itself, as well as larger molecular weight forms of botulinum

toxin. See eg the Abstract on page 587 of DasGupta B., et al., *Role of a protease in natural activation of Clostridium botulinum neurotoxin*, Infect Immun 1972 Oct;6(4):587-90 ("Progenitor toxin [toxic forms whose specific toxicity is increased by treatment with trypsin] was found in culture fluid of all strains…progenitor toxin (molecular weight 150,000)…" (attached as Exhibit E). Hence, the disclosure in the '996 application that "The term Botulinum toxin is a generic term embracing the family of toxins produced by the anaerobic bacterium *Clostridium botulinum*…" is understood by the person of ordinary skill to include the neurotoxic component" as part of this "family of toxins" made by fermentation of the Clostridium bacterium..

Hence, page 2, lines 24-26 of the '996 application provides additional disclosure which is inclusive of the neurotoxic component.

3. Third, in the "Summary of the Invention" on page 5, at lines 16-21 of the '996 application discloses that "The Botulinum toxins appear to be zinc endopeptidases…" (i.e. an enzyme which requires zinc). Clearly, a person of ordinary skill would understand that this means that it is the 150 kD neurotoxic component which is a zinc endopeptidase, for as explained by the prior art:

> BoNTs (botulinum neurotoxins) are produced as 150-kDa single polypeptide chains…We suggest here the possibility that BoNTs are metalloendopeptidases…All clostridial neurotoxins, whose sequences are available, contain the zinc binding motif of zinc endopeptidases. Schiavo G., et al., *Botulinum Neurotoxins are Zinc Proteins*, J Biol Chem 1992 Nov; 267(33): 23479-83 (attached as Exhibit F).

Hence, page 5, at lines 16-21 of the '996 application is a disclosure of a property of the neurotoxic component.

4. Fourth, the biological activity of a botulinum toxin, which is due to the 150 kD neurotoxic component of the botulinum toxin, is "interfering with the

exocytosis of acetylcholine" (page 3, lines 9-10 of the '996 application). Thus the "biological activity " of a botulinum toxin which is referred to on page 5, line 13 of the '996 application (in the "Summary of the Invention") is the biological activity of the neurotoxic component, thereby providing further disclosure in the '996 application of the neurotoxic component.

5. Fifth, in claim 5 the claim limitation "*only a botulinum toxin type A*" is supported by at least page 8, lines 9-13 of the '996 application which disclose use of a single botulinum toxin type, such as a type A botulinum toxin.

6. Sixth, in claim 28, the claim limitation *"the neurotoxic component of a single botulinum toxin type*" is supported by at least page 8, lines 9-13 of the '996 application which disclose use of a single botulinum toxin type.

Thus, as explained in points 1 to 6 above the '996 application clearly discloses that it is the neurotoxic component of a botulinum toxin which is responsible for the biological activity of the botulinum toxin and that the neurotoxic component (in both its single and dichain forms) is within the scope of the invention disclosed in the '996 application.

Finally, while it is true that the '996 application discloses use of the botulinum toxin complex products DYSPORT and BOTOX, this merely teaches that commercial sources for the botulinum toxins can be used, as they comprise the neurotoxic complex. This teaching in the speciation must be appreciated in light of the disclosure on page 3 of the '996 application, namely that the neurotoxic component is the active component and so it is simply one way of utilizing this active component to use commercial preparations such as the complex containing preparations DYSPORT and BOTOX.

C. <u>The Brin Declaration Rebuts the Lack of Written Description Rejection</u>

Attached to this response is a March 28, 2007 declaration from Dr. Mitchell Brin, presented under 37 C.F.R. section 1.132 to assist the prosecution of this

application. Dr. Brin is an acknowledged and renowned botulinum toxin expert and perhaps the world's foremost authority in the therapeutic use of botulinum toxin to treat various disorders. See paragraphs 1-13 of the Brin declaration, including paragraph 13 and attachment A to the Brin declaration.

The Office Action rejected claims 1-5 for lack of written description under section 112(1).

The specific elements of the lack of written description rejection by the Office Action, as set forth on page 3 of the Office Action, are that: (a) the specification is limited to the use of botulinum toxin type A rather than pure botulinum toxin or complex free botulinum toxin; (b) the specification does not teach nor imply that only the neurotoxic component is utilized, and; (c) the specification does not distinguish between a botulinum toxin complex and the neurotoxic component of a botulinum toxin complex. are each rebutted by the Brin declaration as follows:

The Brin declaration provides evidence which directly rebuts each of the bases for the lack of written description rejection made by the office Action. Thus, the Brin declaration provides evidence that:

1. a physician of ordinary ability with knowledge of or experience using a botulinum toxin ("the Physician") would in December 1993 have very clearly realized upon reading the specification that the '996 patent application describes methods for treating various muscle spasms by administration of just the neurotoxic component of a botulinum toxin complex to the patient (Brin Dec. ¶15) (expert opinion statement). See also Brin Dec. ¶19 (expert opinion statement)

2. page 3, lines 5-24 of the '996 application discloses that there is a neurotoxic component of a botulinum toxin. Brin Dec. ¶16(1)(a) (fact statement).

3. page 3, lines 5-24 of the '996 application discloses that the neurotoxic component has a molecular weight of about 150 kD (Brin Dec. ¶16(1)(b) (fact statement);

4. page 3, lines 5-24 of the '996 application discloses that the 150 kD neurotoxic component can be in the form of a dichain, that is comprising a 50 kD short chain and a 100 kD long chain. Brin Dec. ¶16(1)(c) (fact statement);

5. page 3, lines 5-24 of the '996 application discloses that the neurotoxic component is responsible for the toxic properties of a botulinum toxin. Brin Dec. ¶16(1)(d) (fact statement);

6. the matters set forth in items 2. to 5. above were facts already established in the literature and therefore known to the Physician. Brin Dec. ¶16(2) (fact statement).

7. page 3, lines 5-24 of the '996 application discloses that use of the neurotoxic component (in either it's single or dichain forms) is "useful in the method of the present invention" thereby directly and immediately telling the Physician that the neurotoxic component can be used to treat the *inter alia* various types of muscle spasms. Brin Dec. ¶16(3) (fact statement).

8. on page 5, at lines 16-21 of the '996 application it is disclosed that a botulinum toxin is a zinc endopeptidase. The Physician would readily understand this to mean that it is the neurotoxic component of a botulinum toxin is a zinc endopeptidase, and this is taught by the literature as well. Brin Dec. ¶16(4) (fact statement).

Hence, the Brin declaration rebuts and overcomes the lack of written description rejection in the Office Action. In other words, the Brin declaration

presents significant and sufficient factual evidence with direct bearing upon the presence of the required written description of the claimed invention. The Brin declaration is entitled to considerable deference and weight as the opinion of a renowned expert and such a declaration can be sufficient to over overcome a section 112, first paragraph rejection. See eg *In re Alton,* 37 USPQ2d 1578 (Fed Cir. 1996) (attached as Exhibit G). (vacating the decision of the Board of Patent Appeals and Interferences which affirmed the examiner's rejection for lack of written description, stating that the patent examiner had erred in his reasoning which concluded that the expert declaration did not rebut the prima facie rejection of the claims under section 112, first paragraph).

Additionally, when a declaration is submitted to rebut a section 112, first paragraph written description rejection such "Affidavits are inherently material" (*Refac v. Lotus*, 38 USPQ2d 1665 at 1671, left hand side column (Fed Cir. 1996) (attached as Exhibit H).

Thus, the evidence presented by the Brin declaration rebuts the *prima facie* case of lack of written description presented by the Office Action and the rejection of the claims should therefore be withdrawn.

D. The Claims Meet the Legal Standard for Written Description

Written description is a question of fact, judged from the perspective of one of ordinary skill in the art. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). Compliance with § 112 requires sufficient information in the specification to show that the inventor possessed the invention as of the relevant filing date. See Vas-Cath, 935 F.2d at 1563-64 ("[T]he applicant must... convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention."); Union Oil Co. of Cal. v. Atl. Richfield Co., 208 F.3d 989, 997 (Fed. Cir. 2000) ("The written description requirement does not require the applicant 'to describe exactly the subject matter

claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.'" (citation omitted)). The Federal Circuit has stated that the written description requirement may be satisfied by the patentee's disclosure of "such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). More recently, the Federal Circuit has held that "(1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met [ ] even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." Falkner v. Inglis, 79 U.S.P.Q.2d 1001 at 1007 (Fed. Cir. 2006) (emphasis added) . "Certainly no length requirement exists for a disclosure to adequately describe an invention. . . . [T]he adequacy of the description . . . depends on its content in relation to the particular invention, not its length." See In re Hayes Microcomputer Products, Inc. Patent Litigation (Ven Tel, Inc. v. Hayes Microcomputer Products, Inc.), 982 F.2d 1527 (Fed. Cir. 1992).

It has been explained above, as supported by the evidence contained in the Brin declaration, that the '996 application of the present application discloses sufficient information to show that the inventors possessed the claimed invention as of the December 1993 effective filing date of this application, thereby meeting the requirement of section 112, first paragraph for adequate written disclosure of the claimed invention.

E. Summary

To summarize, the '996 application clearly discloses (as further explained and supported by the Brin declaration): (a) the existence of the neurotoxic component of a botulinum, including the molecular weight (about 150 kDa) and single or

dichain forms of the neurotoxic component; (b) that the neurotoxic component is responsible is responsible for the biological activity of a botulinum toxin; (c) that the neurotoxic component is "useful in the method of the present invention", and; (d) that the neurotoxic component can be used by itself to treat a spastic muscle.

In view of the above, the present '996 application clearly discloses that the neurotoxic component by itself is utilized in the claimed method. Accordingly, as the standard for written description is assessed from the viewpoint of one having ordinary skill in the art, the claimed method for treating a spastic muscle that comprises administering a therapeutically effective amount of the neurotoxic component of a botulinum toxin to a patient has more than adequate written description in the '996 application as filed.

Hence, the '996 application does provide a written description of the claimed invention. For these reasons the rejection should be withdrawn with regard to the amended claims.

The '996 Application Provides Section 112, First Paragraph Enablement for Claims 1-2, 4-5 and 29-77, as Amended

A. Introduction

The Office Action denial domestic priority under 35 U.S. section 120 for claims 1 to 5 to the '996 Application for alleged lack of enablement under 35 U.S.C. Section 112, first paragraph.

Thus, pages 3-5 of the Office Action states that the claims lack enabling disclosure for use of pure toxin. Respectfully, the rejection is in error and should be withdrawn

B. The '996 application Enables Making or Obtaining the Neurotoxic Component of a Botulinum Toxin

Page 4, lines 9-12 of the '996 application discloses that botulinum toxin can be obtained by culture, fermentation and purification in accordance with known techniques. By purification of a botulinum toxin (page 4, lines 11-12 of the '996 application) a person of ordinary skill, in view of the claimed invention, understands this to mean obtaining the neurotoxic component by purification from a botulinum toxin complex. See eg paragraph 18(a) of the Brin declaration. With regard to known culture techniques, page 2, line 33 continuing to page 3, line 3 of the '996 application, chapter 1 of Hatheway (1989) was incorporated by reference into the '996 application. Chapter 1 of Hatheway (1989) (attached as Exhibit I) discloses on page 13 (section H) that the bacterium which makes botulinum toxin can be grown on agar at 30-37 C.

With regard to known fermentation techniques, the prior art publication Schantz et al, *Properties and use of botulinum toxin and other microbial neurotoxins in medicine*, Microbiol Rev 1992 Mar; 56(1): 80-89 (attached as Exhibit J) discloses on eg page 82 detailed fermentation methods for obtaining a botulinum toxin.

With regard to known purification techniques for obtaining the neurotoxic component for use in the claimed invention, it was well known before the priority date of this application that botulinum toxin comprises a neurotoxic component in non-covalent association with accompanying non-toxic proteins, and that the neurotoxic component can be easily obtained by subjecting botulinum toxin to alkaline pH conditions, because at a basic pH the non-toxic proteins disassociate from the neurotoxic component and the neurotoxic component can then be easily recovered. See e.g.:

(1) Wagman J. et al., *Botulinum Type A toxin: properties of a toxic dissociation product*, Arch Biochem Biophys 1953; 45: 375-383 (attached as Exhibit K) (parenthesis added):

> This paper will be devoted to a description of the properties of a substance which makes its appearance when solutions of type A botulinum toxin are brought to pH 7.5…the slowly sedimenting component represents a fully active form of the toxin which is free from the hemagglutinin commonly associated with it" (Abstract, page 375). "..the rapidly sedimenting polydisperse component at pH 7.5 will be referred to as the '*complex toxin*' (i.e. the non-toxic complex proteins), the slowly sedimenting polydisperse component as the '*dissociated toxin*' (i.e. the neurotoxic component)" (page 381).

(2) DasGupta B., et al., *Separation of toxin and Hemagglutinin from crystalline toxin of Clostridium botulinum type A by anion exchange chromatography and*

determination of their dimensions by gel filtration, J Biol Chem 1969 Mar 10; 243(5): 1065-72 (attached as Exhibit L):

> Crystalline preparations of *Clostridium botulinum* type A toxin were fractionated on DEAE-cellulose columns with Tris-HCL buffers at pH 8.0…the toxic fragment had a molecular weight of 150,000…" (Abstract).

(3) Schantz E., *Use of crystalline type A botulinum toxin in medical research*, being pages 143-150 of in Lewis G., Biomedical aspects of botulism, Academic Press, New York (1981 (attached as Exhibit M), page 143:

> botulinum toxin "…is a high molecular weight simple protein (about 900,000) and dissociates under certain conditions of pH and ionic strength into a protein of about 150,000 molecular weight having the neurotoxin properties…".

(4) Borodic, G., et al., *Clinical and scientific aspects of botulinum A toxin*, Ophthalm Clinics of N America 1991 Sep; 4(3): 491-503 (attached as Exhibit N), at page 492: "Under slightly alkaline conditions (pH greater than 7.1)…the neurotoxin is released from the toxin complex".

(5) Schantz E., et al., *Properties and use of botulinum toxin and other microbial neurotoxins in medicine,* Microbiol Rev 1992 Mar;56(1):80-99 (attached as Exhibit J)

> " the neurotoxic component of 150,000 M is bound noncovalently to the nontoxic proteins…Under slightly alkaline conditions (>pH 7.1)…the neurotoxin is released from the toxin complex." (page 82, right hand side column).

Furthermore, the neurotoxic component was commercially available from several sources prior to the priority date of this application. See attached Exhibit O which comprises List Biologicals and Sigma Chemicals materials, suppliers of the neurotoxic component in 1993.

Thus, not only was it well known prior to the 1993 priority date of this application that the botulinum toxin complex can be purified to obtain the neurotoxic component, by simply placing the botulinum toxin complex in a mildly alkaline buffer (i.e. pH 7.3 to 8.5) and recovering the neurotoxic component released from its non-covalent association with the botulinum toxin non-toxic proteins, but as well the neurotoxic component was available for commercial purchase. Hence the '996 application in light of the prior art clearly enables a person of ordinary skill to obtain the neurotoxic component of a botulinum toxin without undue experimentation.

C. The '996 application Enables Use of
the Neurotoxic Component of a Botulinum Toxin

It has been explained above that the '996 application describes how to obtain the neurotoxic component of a botulinum toxin. For the purpose of the claimed invention it is irrelevant that the '996 application states on page 4 (in the Background section of the '996 application) that there are commercially available botulinum toxin complex products BOTOX and DYSPORT. What is relevant is that: (a) the '996 application states on page 3 that both the single chain and dichain forms of the neurotoxic component are useful in the invention; (b) page 5 (in the Summary of the Invention section of the '996 application) states that it is the zinc endopeptidase, that is the neurotoxic component, which is responsible for the activity of a botulinum, and; (c) particulars as to how to administer the neurotoxic component are set forth on pages 7-8 of the '996 application (in the Detailed Description section of the '996 application) where the phrase "the toxin" is used to mean either a botulinum toxin (i.e. a botulinum toxin complex) the neurotoxic component, as is evident from the fact that use of both the neurotoxic component and the whole botulinum toxin are disclosed in the '996 application (see eg page 1, lines 7-9 and page 3, lines 23-24 of the '996 application).

Thus, the '996 application in light of what was known to one of ordinary skill in the prior art clearly enables one ordinary skill in the art to obtain the neurotoxic component of a botulinum toxin as to be able to practise the claimed invention without undue experimentation. For theses reasons the rejection should be withdrawn.

D. The Brin Declaration Rebuts the Lack of Enablement Rejection

The Brin declaration provides evidence which directly rebuts the basis for the lack of enablement ejection made by the office Action. Thus, the Brin declaration states:

1. the Physician would upon reading the patent application have been able "with little or no difficulty" to obtain the neurotoxic component to use to treat *inter alia* a spastic muscle. (Brin Dec. ¶17) (expert opinion statement). See also Brin Dec. ¶19 (expert opinion statement).

2. page 4, lines 9-24 of the application in light of the teachings of the prior art discloses that the neurotoxic component could be easily purified from a botulinum toxin complex. Brin Dec. ¶18(a) (fact statement).

3. significantly, the Physician knew in December 1993 that the neurotoxic component could be obtained commercially. (Brin Dec. ¶18(b) (fact statement).

4. pages 7-8 pf the application gives particular as to how to administer the neurotoxic component. Brin Dec. ¶18(c) (fact statement).

Hence, the Brin declaration rebuts and overcomes the lack of enablement rejection in the Office Action.

E. The Claims Meet the Legal Standard for Enablement

The test for enablement is whether one skilled in the art at the time applicants filed the present application could make and use the claimed invention from the disclosures in the specification coupled with the information known in the art without undue experimentation. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991).

Factual considerations that can be weighed when determining whether "undue" experimentation would be required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the relative skill of those in the art, (5) the predictability or unpredictability of the art, (6) the amount of direction or guidance provided, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary. See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Any part of the specification can support an enabling disclosure, including a background section that discusses or even disparages the subject matter disclosed therein. Callicrate v. Wadsworth Mfg., Inc., 427 F.3d 1361, 1374 (Fed. Cir. 2005). All the evidence must be considered, and any conclusion of nonenablement must be based on the evidence as a whole. MPEP § 2164.01(a).

Applicants respectfully submit that an analysis of all the relevant evidence reveals that applicant's '996 application as filed is such that one of ordinary skill in the art would have been able to make and use the claimed invention without undue experimentation, as further explained below.

The *In re Wands* forth set forth above can be reviewed to assist an evaluation of enablement of the claimed subject matter:

1. *Nature of the Invention*

The claimed invention is a method for treating a spastic muscle using the neurotoxic component of a botulinum toxin. The '996 application provides more than sufficient guidance to one of ordinary skill regarding the claimed invention. For example, the '996 application provides guidance at page 4, lines 9-12, regarding known techniques to purify botulinum toxins. The '996 application provides guidance at page 4, lines 14-19, regarding botulinum toxins that are available from commercial sources, and provides examples of such sources. Other commercial sources include Sigma Chemical Co., from which one of ordinary skill could have obtained type A neurotoxic component as product number B8776. See, 1993 Sigma Chemical catalog pages attached hereto as Exhibit O. The '996 application also provides guidance at page 7, line 11 to page 8, line 10 regarding techniques for administering purified neurotoxic component.

2. *State of the Prior Art*

The state of the art, as set forth above was that it was well known how to obtain the neurotoxic component of a botulinum toxin without undue experimentation. Thus, for example, one of ordinary skill would have known that the neurotoxic component, either single chain or dichain, was obtained by fermentation of Clostridium botulinum followed by simple purification steps. See Brin Declaration ¶18(a). One of ordinary skill would have known that neurotoxic component was available for purchase from commercial suppliers. See Brin Declaration ¶18(b). One of ordinary skill would have known the techniques for administration of the neurotoxic component, e.g., by intramuscular administration. See the Brin Declaration at ¶18(c).

The Schantz (1992) article cited on page 4 of the Office Action states on page 89 that "it is unlikely that [the neurotoxic component] will be used in a clinical setting." However, Schantz (1992) do not characterize the state of the art as bleak. Rather, Schantz indicates a long felt need for other botulinum toxin types

for clinical use ("…it is likely that types other than type A will be used clinically…") (page 86, left hand side column).

3. *Relative Skill of those in the Art*

The relative skill in those in the art was high.

4. *Predictability of the Art*

It was well known to the prior art that the neurotoxic component is the biologically active component of a botulinum toxin. See Brin declaration ¶16., Therefore the predictability of therapeutic efficacy upon use of the neurotoxic component must be considered to be high or very predictable.

5. *Breath of the Claims*

The breadth of the claims is narrow because the claims are limited to treatment of a spastic muscle using a specific active agent, the neurotoxic component of a botulinum toxin.

6 and 7. *Guidance Provided and Presence of Working Examples*

The '996 application discloses at page 4, lines 9-12 that a botulinum toxin can be purified (i.e. so as to obtain the neurotoxic component) and then stabilized and preserved (see eg page 7, lines 21-28 of the '996 application). Additionally, the claimed invention is directed to a method in which the neurotoxic component administered has been obtained by the purification of a botulinum toxin provided by fermentation of a Clostridium botulinum. And as explained in paragraph 18 of the Brin declaration the '996 application provides guidance to one of ordinary skill, in light of the teachings of the prior art, as to how to obtain the neurotoxic component used in the claimed method without undue experimentation.

Additionally, the '996 application discloses the different components of a botulinum toxin and clearly indicates that one can use the neurotoxic; see eg

page 3, lines 23-25 that both forms (single and dichain) of the neurotoxic component "are useful in the method of the present invention".

Regarding examples, the '996 application explicitly states at page 3, lines 23-24 that the neurotoxic component of a botulinum toxin can be used in the methods of the invention. Hence, it cannot be clearer that the Examples of the invention on pages 10-20 of the '996 application all encompass use of the neurotoxic component.

8. *Quantity of Experimentation Necessary*

In view of the above, the weight of all the evidence indicates that one of ordinary skill in the art would have been able to make and use the claimed invention without undue experimentation, based on the present '996 application and knowledge of the prior art.

It would appear that no experimentation would be required by one of ordinary skill to practice the claimed invention because (a) it was known to the person of ordinary skill in 1993 that the neurotoxic component of a botulinum toxin could be obtained by simply running a botulinum toxin complex through a protein separation resin in an alkaline pH buffer and furthermore the neurotoxic component of a botulinum toxin was available for purchase simply by ordering it from a commercial supplier, such as Sigma. See Brin Declaration paragraph 18(a) and (b).

Hence, the '996 application clearly does enable one of ordinary skill in the art to practise the claimed invention with undue experimentation. As explained above, the '996 application does clearly teach how to make and how use the neurotoxic component of a botulinum toxin in the claimed invention. All the person of ordinary skill had to do as of the December 1993 priority date of this patent application in order to obtain the neurotoxic component of a botulinum

toxin was carry out a simple elution procedure of the botulinum toxin in an alkaline buffer or just pick up the phone and call a commercial supplier of the neurotoxic component.

For these reasons the lack of enablement rejection by the Office Action should be withdrawn.

V. Section 103(a) Rejection of Claims 1-5

The Office Action rejected claims 1-5 under 35 U.S.C. section 103(a) as being unpatentable over Balkan (1991) or Han (2001) in view of Tse (1982) and Aoki (U.S. patent 6,113,915 filed in 1999). Respectfully, the rejection is in error and should be withdrawn for at least the following reasons:

1. Applicants have argued above and have presented evidence that the claims as amended are entitled to priority to the December 28, 1993 filing date of the '996 application. If applicants are granted the requested priority, the Han article (published in 2001) and the Aoki patent (filed in 1999) are not prior art with regard to the amended claims, thereby obviating and rendering moot a rejection of the claims over the combination of Balkan or Han in view of Tse and Aoki.

2. A combination of the remaining references in the rejection, Balkan (1991) and Tse (1982), cannot create a *prima facie* case of obviousness of the amended claims obvious because Schantz, *Properties and use of botulinum toxin and other microbial neurotoxins in medicine*, Microbiol Rev 1992 Mar; 56(1): 80-89 (1992) discloses on page 89 that "it is unlikely that [the neurotoxic component] will be used in a clinical setting", thereby showing that the prior art teaches away from a combination of Tse with Balkan to thereby allegedly obtain the claimed invention.

It is well settled that a *prima facie* case of obviousness is only established if there is some suggestion or motivation to combine prior art references, and the teaching or suggestion to make the combination, together with the reasonable expectation of success, must both be found in the prior art as a whole, not based on Applicant's own disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). This requirement has been established to prevent the improper use of hindsight combinations of prior art. To prevent such hindsight combinations, Federal

Circuit case law "requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the matter claimed." *In re Rouffet*, 47 USPQ2d 1453, 1457-1458 (Fed. Cir. 1998). Applicants submits that no motivation to combine the Balkan and Tse references can exist. Thus, in light of the Schantz (1992) article, which is more nearly concurrent to the 1993 filing date of the '996 application as compared to the 1982 Tse article, there would have been no motivation to combine Balkan and Tse and certainly in view of Schantz (1992) no expectation of reasonable success if the combination was made.

For these reasons the rejection should be withdrawn.

V. Section 103(a) Rejection of Claims 1-5

The Office Action rejected claims 1-5 under 35 U.S.C. section 103(a) as being unpatentable over Balkan (1991) or Han (2001) in view of Aoki (U.S. patent 6,113,915 filed in 1999) and Aoki (2001 018415). Respectfully, the rejection is in error and should be withdrawn for at least the following reason:

Applicants have argued above and have presented evidence that the claims as amended are entitled to priority to the December 28, 1993 filing date of the '996 application. If applicants are granted the requested priority, the Han article (published in 2001) and the Aoki patent (filed in 1999) are not prior art with regard to the amended claims. Additionally, Aoki (2001 018415) as a divisional application having the same specification and same effective filing date as the '996 application, also cannot be prior art with regard to the amended claims. Hence, if priority to the December 28, 1993 filing date of the '996 application is granted the rejection is obviated and renders moot a rejection of the claims over the combination of over Balkan or Han (2001) in view of Aoki (U.S. patent 6,113,915) and Aoki (2001 018415).

For these reasons the rejection should be withdrawn.

VI. New Claims 29-77

New claims 29-77 are in condition for allowance because claims 29-77 are supported by the '996 application and are free of the art.

A. New claims 29-77 are supported by the '996 application at least because:

(1) claim 29: the claim limitation "*a method for treating a spastic muscle"* is supported by at least page 10, line 23-24 which discloses treating a spastic facial muscle; page 13, line 26 and page 19, line 11 for treating a spastic hand muscle; page 13, line 26 for treating a spastic head muscle; page 11, line 25 for treating a spastic neck muscle; page 15, line 6 for treating a spastic vocal cord muscle; Example 6 on page 17, at lines 9-25 for treating a spastic smooth muscle, which can be eg a spastic smooth muscle sphincter of the gastrointestinal, urinary or rectal system; page 17, line 35 continuing to page 18, line 1 for treating a spastic jaw muscle; page 18, line 12 for treating a spastic thigh muscle; Example 9 on page 19 at lines 1-15 for treating a spastic wrist, forearm, or leg muscle, and; page 19, line 22 and page 20, line 6 for treating a spastic throat muscle.

(2) claim 29: the claim limitation " *administering to a human patient a therapeutically effective amount of the neurotoxic component of a single botulinum toxin type to thereby treat the spastic muscle* is supported by at least:

(a) The Examples on pages 10-20 of the '996 application (treatment of various spastic muscles), and;

(b) page 3, lines 5-24 of the '996 application (the neurotoxic component is useful in the method of the present invention").

(3) claim 29: the claim limitation "*wherein neurotoxic component administered to the patient has been purified from a botulinum toxin obtained by fermenting a*

Clostridium botulinum" is supported by at least page 3, lines 5-10 of the '996 application ("The neurotoxic component of botulinum toxin…is considered to be responsible for the toxic properties of the botulinum toxin…"); page 3, lines 23-24 of the '996 application (the neurotoxic component is useful in the method of the present invention"), and; page 4, lines 9-12 of the '996 application ("Botulinum toxin is obtained commercially by…purifying the fermented mixture in accordance with known techniques").

(4) claim 29: the claim limitation "*single botulinum toxin type*" is supported by at least page 8, lines 9-13 of the '996 application which disclose use of a single botulinum toxin type.

(5) claim 29: use of botulinum toxins types A, B, C, D, E, F or G is supported by at least page 2 lines 28-29 of the '996 application ("These have been given the designations A, B, C, D, E, F and G.").

(6) claims 30, 46 and 62: the claim limitation "*about 150 kilodaltons*" is supported by at least page 3, lines 5-6 of the specification.

(7) claim 31, 47 and 63: the claim limitation "*by intramuscular injection*" is supported by at least page 7, lines 11-12.

(8) claims 32, 48 and 64: the claim limitation "*a facial muscle*" is supported by at least page 10, line 23-24 ("facial muscles").

(9) claims 33, 49 and 65: the claim limitation "*a jaw muscle*" is supported by at least page 17, line 35 continuing to page 18, line 1 ("the muscles controlling closure of the jaw").

..

(10) claims 34, 50 and 66: the claim limitation "*a throat muscle*" is supported by at least page 19, lines 22 and page 20, line 6 ("throat muscle spasms).

(11) claims 35, 51 and 67: the claim limitation "*a vocal chord muscle*" is supported by at least page 15, line 6 ("spasm of the vocal cords").

(12) claims 36, 52 and 68: the claim limitation "*a leg muscle*" is supported by at least page 19, line 12 ("muscles involved in the closing of the legs").

(13) claims 37, 53 and 69: the claim limitation "*a thigh muscle*" is supported by at least page 18, line 12 ("cramping in thigh").

(14) claims 38, 54 and 70: the claim limitation "*a hand muscle*" is supported by at least page 13, line 26 ("hand muscles") and page 19, line 11 ("muscles involved in severe closing of hand").

(15) claims 39, 55 and 71: the claim limitation "*a wrist muscle*" is supported by at least page 19, lines 10-11 ("muscles involved in…curling of wrist").

(16) claims 40, 56 and 72: the claim limitation "*a forearm muscle*" is supported by at least page 19, lines 10-11 ("muscles involved in…forearm).

(17) claims 41, 57 and 73: the claim limitation "*a smooth muscle*" is supported by at least page 17, lines 11-12 ("muscle spasms in smooth muscle disorders").

(18) claims 42, 58 and 74: the claim limitation " *a sphincter*" is supported by at least page 17, lines 11-12 ("muscle spasms in smooth muscle disorders such as sphincters").

(19) claims 43, 59 and 75: the claim limitation "*a gastrointestinal system smooth muscle sphincter*" is supported by at least page 17, lines 10-12 ("muscle spasms in smooth muscle disorders such as sphincters of the…gastrointestinal system").

(20) claims 44, 60 and 76: the claim limitation "*a urinary smooth muscle sphincter*" is supported by at least page 17, lines 10-12 ("muscle spasms in smooth muscle disorders such as sphincters of the…urinary" system).

(21) claims 45, 61 and 77: the claim limitation "*a rectal sphincter*" is supported by at least page 17, lines 10-12 ("muscle spasms in smooth muscle disorders such as sphincters of the…rectal" system).

Additionally, the '996 application discloses that the neurotoxic component is responsible for the toxic properties of a botulinum toxin and that a botulinum toxin can be cultured, fermented and purified according to "known techniques." The "known techniques" referred to in the '996 application included known culture techniques (see page 3, lines 16-20 of the '996 application which incorporates by reference, chapter 1 of Hatheway (1989) (attached as Exhibit I) which discloses on page 13 that the bacterium which makes botulinum toxin can be grown on agar at 30-37 C.), and for known fermentation techniques (see eg Borodic G., et al *Clinical and scientific aspects of botulinum A toxin,* Ophthalm Clinics of N America 1991 Sep;4(3):491-503 (attached as Exhibit N) which discloses at pages 492-493 a detailed fermentation method for obtaining a botulinum toxin).

Significantly, the "purifying" by "known techniques" disclosed by the parent application includes known methods for purifying the neurotoxic component from a botulinum toxin. See eg:

(a) Wagman J. et al., *Botulinum Type A toxin: properties of a toxic dissociation product*, Arch Biochem Biophys 1953; 45: 375-383, at page 381 (attached as Exhibit K) (parenthesis added):

> This paper will be devoted to a description of the properties of a substance which makes its appearance when solutions of type A botulinum toxin are brought to pH 7.5…the slowly sedimenting component represents a fully active form of the toxin which is free from the hemagglutinin commonly associated with it" (Abstract, page 375). "..the rapidly sedimenting polydisperse component at pH 7.5 will be referred to as the '*complex toxin*' (i.e. the non-toxic complex proteins), the slowly sedimenting polydisperse component as the '*dissociated toxin*' (i.e. the neurotoxic component)".

(b) DasGupta B., et al., *Separation of toxin and Hemagglutinin from crystalline toxin of Clostridium botulinum type A by anion exchange chromatography and determination of their dimensions by gel filtration*, J Biol Chem 1968 Mar 10; 243(5): 1065-72 (attached as Exhibit L):

> Crystalline preparations of *Clostridium botulinum* type A toxin were fractionated on DEAE-cellulose columns with Tris-HCL buffers at pH 8.0…the toxic fragment had a molecular weight of 150,000…" (Abstract).

(c) Schantz E., *Use of crystalline type A botulinum toxin in medical research*, being pages 143-150 of in Lewis G., Biomedical aspects of botulism, Academic Press, New York (1981) (attached as Exhibit M), at page 143:

> botulinum toxin "…is a high molecular weight simple protein (about 900,000) and dissociates under certain conditions of pH and ionic strength into a protein of about 150,000 molecular weight having the neurotoxin properties…".

(d) Borodic, G., et al., *Clinical and scientific aspects of botulinum A toxin*, Ophthalm Clinics of N America 1991 Sep; 4(3): 491-503 (attached as Exhibit n),

at page 492: "Under slightly alkaline conditions (pH greater than 7.1)...the neurotoxin is released from the toxin complex".

Thus, "in accordance with the known techniques" (page 4, line 8) disclosed in the '996 application of this application it was well known prior to the December 1993 priority date of this application that the botulinum toxin complex can be purified to obtain the neurotoxic component simply placing the botulinum toxin complex in an alkaline buffer and recovering the neurotoxic component released from its non-covalent association with the botulinum toxin non-toxic proteins. Hence the claim limitation "*wherein the neurotoxic component has been purified from a botulinum toxin obtained by fermenting a Clostridium botulinum"* in the claims is fully described and enabled by the '996 application in light of the prior art because a person of ordinary skill could from reading the patent application and with a knowledge of the prior art could obtain the neurotoxic component of a botulinum toxin without undue experimentation to practise the claimed method. See also paragraph 18 of the Brin declaration.

B. New claims 10-20 are free of the cited art at least because Han (2001) and both Aoki references are not prior art with regard to the amended claims and Balkan (1991) and Tse (1982), cannot be combined to render any of claims 29-77 obvious because Schantz, *Properties and use of botulinum toxin and other microbial neurotoxins in medicine*, Microbiol Rev 1992 Mar; 56(1): 80-89 (1992) discloses on page 89 (Exhibit J) that "it is unlikely that [the neurotoxic component] will be used in a clinical setting", thereby teaching away a combination of Tse with Balkan to achieve the subject matter of any of claims 29-77.

Hence new claims 29-77 are in condition for allowance.

VII. Conclusion

All issues raised in the Office Action have been addressed. Examination and allowance of claims 1-2, 4-5 and 29-77 is requested.

Respectfully submitted,

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